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Multiple Sclerosis- New Approaches and Treatment Strategies

M Cholakova*, N Mihnev and Iv Staykov

Acibadem City Clinic University Hospital Tokuda, Department of Neurology, Bulgaria

***Corresponding author:** M Cholakova, Acibadem City Clinic University Hospital Tokuda, Department of Neurology, Bulgaria

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ABSTRACT

Multiple sclerosis is a socially significant, disabling autoimmune disease that predominantly affects young adults. Rapid initiation of immunomodulatory therapy is necessary in order to reduce the risk of disease progression. Early use of highly effective therapy should be considered from the very onset of the disease. The optimal strategy is that of personalized medicine, taking into account the individual preferences and life plans of each patient. A critical evaluation of the available evidence is required before making a decision regarding the best possible treatment.

Keywords: Multiple Sclerosis; Escalation Therapy; High-Efficacy Therapy

Abbreviations: MS: Multiple Sclerosis; CNS: Central Nervous System; EBV: Epstein–Barr Virus; EBV: Epstein–Barr Virus; MRI: Magnetic Resonance Imaging; CIS: Clinically Isolated Syndrome; RRMS: Relapsing–Remitting MS; PPMS: Primary Progressive MS; SPMS: Secondary Progressive MS; AEM: Autoimmune Encephalomyelitis; DMTs: Disease-Modifying Therapies; ECTRIMS: European Committee for Treatment and Research in Multiple Sclerosis; EAN: European Academy of Neurology; AAN: American Academy of Neurology; IFNs: Interferons; GA: Glatiramer Acetate; TFN: Teriflunomide; DMF: Dimethyl Fumarate; S1P: Sphingosine-1-Phosphate Receptor Modulators; SPMS: Secondary Progressive MS; CNS: Central Nervous System; EAE: Autoimmune Encephalomyelitis; EDSS: Expanded Disability Status Scale

Epidemiology

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system (CNS), affecting more than two million people worldwide [1]. Epidemiologically, MS is a heterogeneous disease influenced by genetic factors—such as the association with HLA-DRB1*15:01—as well as environmental factors including vitamin D levels, obesity, smoking, and Epstein–Barr virus (EBV) infection [2]. The diagnosis is established on the basis of a clinical syndrome combined with evidence of dissemination of lesions in space and time. The revised 2017 McDonald criteria allow for an earlier diagnosis in the setting of a single clinical attack, supported by magnetic resonance imaging (MRI) findings of symptomatic or asymptomatic gadolinium-enhancing T1 or non-enhancing T2 lesions typical of MS and/or the presence of cerebrospinal fluid oligoclonal bands [3]. Clinical subtypes include clinically isolated syndrome (CIS), relapsing–remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) [3]. More recent refinements in MS subtype classification, proposed by Lublin et al., follow a similar framework with additional modification of MS subtypes as “active” or “inactive” based on the presence of clinical relapses and/or MRI activity [4]. There is increasing evidence that the MS phenotype (relapsing versus progressive) is likely determined by “host factors,” most notably patient age, with younger patients experiencing a higher relapse frequency, while older patients are more likely to exhibit progressive phenotypes [5].

Pathogenesis

Alterations in the peripheral immune system, increased permeability of the blood–brain barrier, and the activity of resident immune cells of the CNS (such as microglia) all contribute to the pathogenesis of multiple sclerosis (MS). Current therapeutic strategies are directed toward these three key elements of MS pathogenesis. Both acute and chronic inflammation, as well as neurodegeneration, occur during the course of the disease, with acute inflammation predominating in the relapsing phase. The inflammatory process in MS has been studied in experimental animal models of autoimmune enceph-

alomyelitis (AEM) and through pathological observations in patients with MS, demonstrating the involvement of both innate and adaptive immune responses [6]. Innate immune cells implicated in MS include myeloid-derived macrophages and microglia. Adaptive immune cells involved in MS include autoreactive CD4+ T cells, particularly Th1 cells directed against myelin proteins, as well as CD8+ cytotoxic T cells [7]. Recent studies examining specific T-cell subtypes in patients with MS have identified distinct myelin targets that may correlate with different patterns of inflammation [8]. Although B cells have not been shown to be critical for AEM in animal models, they play a central role in the pathogenesis of human MS through the production of proinflammatory cytokines and chemokines, antibody formation, and antigen presentation to T cells [9].

The presence of oligoclonal bands in the cerebrospinal fluid and antibody–complement deposition in MS lesions further implicates mature B cells in both relapsing and progressive forms of the disease [10]. Although MS lesions are classically recognized as areas of white matter demyelination, inflammatory damage also involves gray matter and subpial/meningeal layers [11]. Progressive MS is thought to result from cumulative damage due to chronic inflammation and neurodegeneration arising from multiple pathogenic mechanisms, including activated microglia, leptomeningeal inflammatory infiltrates causing subpial demyelination, mitochondrial dysfunction, and oxidative damage mediated by macrophages and microglia [12].

Therapeutic Targets

Given the heterogeneity of the disease, there is no single therapeutic target in MS. The primary goal of current disease-modifying therapies (DMTs) is to slow disease progression by reducing inflammation, myelin damage, and relapse frequency. A meta-analysis has demonstrated that all evaluated DMTs reduce relapse rates within two years of treatment initiation [13]. Cohort studies indicate that earlier initiation of DMTs reduces disability accumulation and that early use of high-efficacy therapies may be more effective than traditional escalation approaches [14]. Treatment of progressive MS remains challenging, further suggesting that MS pathogenesis evolves from a predominantly proinflammatory relapsing stage to a neurodegenerative stage that is less responsive to immune-based therapies.

Disease-Modifying Therapies: When to Initiate, which Drug to Choose, and when to Discontinue?

The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), the European Academy of Neurology (EAN), and the American Academy of Neurology (AAN) published guidelines in 2018 for the pharmacological treatment of people living with MS [15]. For patients with clinically isolated syndrome (CIS), the ECTRIMS/EAN guidelines recommend interferon or glatiramer acetate in individuals with abnormal MRI findings suggestive of MS, even if full diagnostic criteria are not met. The AAN recommends annual MRI monitoring during the first five years prior to initiating DMTs to screen for new disease activity. Two main therapeutic strategies are currently used in the management of MS: Escalation therapy, involving a stepwise transition to more effective treatments in response to disease activity; and Early high-efficacy therapy, which involves the use of highly effective agents from the time of diagnosis. Therapeutic options include medications requiring frequent administration—characterized by low to moderate risk of adverse effects but also low to moderate efficacy—such as interferons (IFNs), glatiramer acetate (GA), teriflunomide (TFN), dimethyl fumarate (DMF), and sphingosine-1-phosphate receptor modulators (S1P). Intermittent dosing strategies involve agents administered at longer intervals and are associated with higher efficacy, including natalizumab (NTZ) and anti-CD20 therapies such as ocrelizumab. Induction therapies are characterized by long-lasting effects following short treatment courses; these include cladribine and alemtuzumab (CLD, ALTZ).

While highly effective, these therapies may require retreatment if disease reactivation occurs [16]. Patients should be offered all reasonable DMT options appropriate for their individual clinical profile, taking into account comorbidities, disease severity, specific adverse effect profiles, treatment adherence and accessibility, and reproductive plans. The optimal approach is personalized medicine. A critical appraisal of the available evidence is essential before making treatment decisions for each individual patient. From the perspective of relative efficacy among different DMTs, although no head-to-head trials comparing all available therapies exist, several real-world studies have attempted to evaluate comparative effectiveness in reducing relapse rates and delaying conversion to secondary progressive MS (SPMS) in patients with relapsing MS.

Pathogenesis

Alterations in the peripheral immune system, increased permeability of the blood–brain barrier, and the involvement of resident immune cells of the central nervous system (CNS), such as microglia, contribute to the pathogenesis of multiple sclerosis (MS). Current therapeutic strategies target these three key elements of MS pathogenesis. Both acute and chronic inflammation, as well as neurodegeneration, occur during the disease course, with acute inflammation predominating during the relapsing phase. The inflammatory process in MS has been extensively studied in experimental animal models of autoimmune encephalomyelitis (EAE) and through pathological observations in patients with MS, demonstrating the role of both innate and adaptive immune responses [6]. Innate immune cells involved in MS include myeloid-derived macrophages and microglia. Adaptive immune cells implicated in MS include autoreactive CD4+ T cells, particularly Th1 cells directed against myelin proteins, as well as CD8+ cytotoxic T cells [7]. Recent studies of specific T-cell subtypes from patients with MS have identified different myelin targets that may correlate with distinct inflammatory patterns [8]. Although B cells have not been proven to be critical in EAE animal models, they play a key role in the pathogenesis of human MS through the production

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Disease-Modifying Therapies: When to Initiate, which Agent to Choose, and when to Discontinue?

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Patients should be informed of all reasonable DMT options tailored to their individual circumstances, considering comorbidities, disease severity, specific adverse effect profiles, treatment adherence and accessibility, and reproductive plans. The optimal strategy is personalized medicine. A critical appraisal of available evidence is required before making treatment decisions for each individual patient.

Injectable vs Oral vs High-Efficacy DMTs

A multicenter retrospective study from the Italian MS registry compared relapse rates and time to first relapse in 3,919 patients treated with first-line injectable DMTs (IFN or GA) and 683 patients treated with first-line oral DMTs (DMF and TRF) [17]. Oral DMTs were associated with lower annualized relapse rates but no difference in disability progression. A comparative effectiveness study using MS registry data and electronic health records evaluated relapse outcomes in patients treated with DMF, S1P modulators, NTZ, and rituximab [18]. No significant differences in relapse rates were observed between DMF and S1P therapies.

Transition to Secondary Progressive MS (SPMS)

An international cohort study of 1,555 patients from MSBase evaluated the risk of conversion to SPMS among patients treated with IFNs, GA, TFN, S1P, NTZ, and alemtuzumab (AMT) [14]. All therapies delayed progression to SPMS compared with untreated patients. The 5-year absolute risk was 12% for IFN or GA, 7% for S1P, 19% for NTZ, and 7% for AMT. Patients who switched from IFN or GA to S1P, NTZ, or AMT within five years had an 8% absolute risk of progression to SPMS. Although newer DMTs demonstrate higher efficacy than older injectable therapies, it remains uncertain whether early initiation of high-efficacy DMTs alters relapse-independent disease progression, as immunotherapy is less effective in progressive MS. Ongoing trials, including TREAT-MS and DELIVER-MS, are investigating early aggressive versus traditional treatment strategies.

Discontinuation of DMTs

As patients enter the neurodegenerative stage of MS, overall inflammatory activity declines, and the effectiveness of DMTs targeting active inflammation diminishes over time, particularly in patients with prolonged disease stability. Considerations for discontinuation include increasing risks of adverse effects with age, accumulating comorbidities, and the financial burden of continued therapy [18]. Available evidence for discontinuation is largely based on retrospective analyses. A meta-analysis of 38 clinical trials demonstrated that

high-efficacy DMTs are most beneficial in younger patients with early disease but provide limited benefit in patients older than 53 years [18]. A retrospective observational study from the Cleveland Clinic involving 600 MS patients over 60 years of age found that 29.7% discontinued DMTs; among them, 89% remained off treatment, with only one clinical relapse reported. No differences were observed in the 25-foot walk test or nine-hole peg test between patients who continued or discontinued therapy [18]. There is currently no consensus definition of disease stability. Suggested criteria include more than five years of clinical stability, absence of relapses and new MRI lesions, and stability in Expanded Disability Status Scale (EDSS) scores.

Conclusion

Over the past three decades, treatment options for MS have expanded rapidly, with significant improvements in relapse prevention. Despite advances in understanding MS pathogenesis, effective treatment for the progressive phase of the disease remains limited. Although newer DMTs offer greater efficacy in reducing relapses and MRI activity, they may carry higher risks of adverse events due to increased immunosuppression.

The heterogeneity of MS, influenced by genetic and environmental factors and the evolving nature of the immune system with age, presents ongoing therapeutic challenges. Promising developments include neuroprotective and remyelinating therapies targeting mitochondrial function and cell-based approaches aimed at drivers of chronic inflammation. Additional strategies involve modulation of immunoprotective mechanisms, such as regulatory T-cell function and reparative microglial activity. Further research is needed to identify early risk factors for heightened inflammatory activity, early neurodegeneration, or their combination. Early therapeutic interventions addressing both neuroinflammatory and neurodegenerative aspects of MS, applied in tandem, are likely essential for future therapeutic progress and the ultimate goal of achieving true disease remission.

References

1. Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer Gould A, et al. (2019) The prevalence of MS in the United States: a population-based estimate using health claims data. Neurology 92(10): e1029-e1040.
2. Ascherio A, Munger KL (2016) Epidemiology of multiple sclerosis: from risk factors to prevention-an update. Semin Neurol 36(2): 103-114.
3. Reich DS, Lucchinetti CF, Calabresi PA (2018) Multiple sclerosis. N Engl J Med 378(2): 169-180.
4. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, et al. (2014) Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83(3): 278-286.
5. Waubant E, Lucas R, Mowry E, Graves J, Olsson T, et al. (2019) Environmental and genetic risk factors for MS: an integrated review. Ann Clin Transl Neurol 6(9): 1905-1922.
6. Kipp M, van der Star B, Vogel DYS, Puentes F, van der Valk P, et al. (2012) Experimental *in vivo* and *in vitro* models of multiple sclerosis: EAE and beyond. Mult Scler Relat Disord 1(1): 15-28.
7. Cruciani C, Puthenparampil M, Tomas Ojer P, Jelcic I, Docampo MJ, et al. (2021) T-Cell specificity influences disease heterogeneity in multiple sclerosis. Neurology - Neuroimmunology Neuroinflammation 129: 43-58.
8. Comi G, Bar Or A, Lassmann H, Uccelli A, Hartung H P, et al. (2021) Expert panel of the 27th annual meeting of the european charcot foundation. Role of B cells in multiple sclerosis and related disorders. Ann Neurol 89: 13-23.
9. Michel L, Touil H, Pikor NB, Gommerman JL, Prat A, et al. (2015) B Cells in the multiple sclerosis central nervous system: trafficking and contribution to CNS-compartmentalized inflammation. Front Immunol 6: 636.
10. Popescu BFG, Lucchinetti CF (2012) Meningeal and cortical grey matter pathology in multiple sclerosis. BMC Neurol 12: 11.
11. Correale J, Gaitán MI, Ysrraelit MC, Fiol MP (2017) Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain 140(3): 527-546.
12. Li H, Hu F, Zhang Y, Li K (2020) Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. J Neurol 267: 3489-3498.
13. He A, Merkel B, Brown JWL, Zhovits Ryerson L, Kister I, et al. (2020) Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. Lancet Neurol 19(4): 307-316.
14. Montalban X, Gold R, Thompson AJ, Otero Romero S, Amato MP, et al. (2018) ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler 24(2): 96-120.
15. Rae Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, et al. (2018) Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology. Neurology 90(17): 777-788.
16. Spelman T, Magyari M, Fredrik Piehl, Anders Svenningsson, Peter Vestergaard Rasmussen, et al. (2020) Treatment Escalation vs Immediate Initiation of Highly Effective Treatment for Patients with Relapsing-Remitting Multiple Sclerosis: Data From 2 Different National Strategies. JAMA Neurol 78(10): 1197-1204.
17. Hou J, Kim N, Cai T, Dahal K, Weiner H, et al. (2021) Comparison of dimethyl fumarate vs fingolimod and rituximab vs natalizumab for treatment of multiple sclerosis. JAMA Network Open 4(11): e2134627.
18. Hartung H P, Meuth SG, Miller DM, Comi G (2021) Stopping disease-modifying therapy in relapsing and progressive multiple sclerosis. Curr Opin Neurol 34(4): 598-603.

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M Cholakova. Biomed J Sci & Tech Res

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